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10/773,773	02/05/2004	Timothy F. Kowalik	UMY-079	8486

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,773	KOWALIK, TIMOTHY F.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *8-26,31-37,46 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,27-30,38-45,47-50,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-17-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with partial traverse of claims 1-7, 27-30, 38-44, SEQ ID NO:2, and CMV gene of IE2 in the reply filed on March 23, 2007 is acknowledged. The traversal is on the ground(s) that different target CMV genes belong to the same search class and subclass, and thus a literature search is coextensive, therefore not imposing an undue burden on the examiner. This is not found persuasive because the different target CMV genes require different search terms and a thorough search of prior art for all recited "six" different CMV genes would impose a serious search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 1-53 are now pending. Applicant has added claims 45-53, of which only claims 45, 47-50, 52, and 53 read on the elected invention. Therefore, claims 8-26, 31-37, 46, 51, 1E1, DNA polymerase, a scaffold protease, gB, and gH are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Accordingly, claims 1-7, 27-30, 38-45, 47-50, and 52-53 pertaining to IE2 and SEQ ID NO:2 are currently under examination on the merits.

Specification

The title of the invention is not descriptive. Currently, this application is titled "RNAi targeting of viruses"; however, the claimed invention in the instant application is exclusively directed to RNAi targeting of a "cytomegalovirus (CMV)". A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

Claims 38- 44 are objected to for depending from a non-elected claim, claim 51. Appropriate correction is required.

Claims 28 and 45 are objected to for containing non-elected subject matter. The claims are also objected to because of spelling or typographical errors. It appears that "1E1" and "1E2" should be "IE1" and "IE2", as evidenced by the disclosure of the specification (page 1). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 38-45, and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting a CMV in a cell infected with CMV comprising administering an RNAi agent targeted to IE2 *in vitro*, does not reasonably

provide enablement for a method of inhibiting a CMV in a subject infected with CMV administering an RNAi agent targeted to IE2 *in vivo,* or treating retinitis in a mammal, or a pharmaceutical composition comprising the RNAi agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The instant specification provides only *in vitro* working examples wherein siRNAs targeted to IE2 gene of HCMV reduce the IE2 gene expression in HCMV-infected cells; however, it is silent about *in vivo* working examples wherein the same siRNAs can be used as a pharmaceutical composition to treat a condition associated with CMV infection (e.g., retinitis) in a vertebrate mammal.

The lack of working examples commensurate with the scope of the claims provided in the specification prompts the question whether the state of the prior art, the level of one of ordinary skill in the art, and the level of predictability of siRNA pharmaceutical compositions in the art would have necessitated undue experimentation for one of ordinary skill in the art to make and use the claimed product as of February 5, 2003, which is the earliest filing date sought in the instant application.

As of the earliest filing date sought in the instant application, treating any viral infection in a vertebrate mammal via nucleic acid molecules was considered highly unpredictable. See Opalinska et al. (*Nature Reviews,* 2002, 1:503-514).

On page 511, Opalinska et al. teach the unpredictability of nucleic acid molecules to modulate the expression of their intended targets *in vivo* as following:

"Nucleic-acid-mediated gene silencing has been used with great success in the laboratory, and this strategy has also generated some encouraging results in the clinic. Nevertheless, it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA....Accordingly, mRNA targeting is largely a random process, which accounts for the many experiments in which the addition of an antisense nucleic acid yields no effect on expression."

Further, the unpredictability of *in vivo* inhibitory activity, let alone therapeutic efficacy, of siRNA molecules remained unresolved as of March, 2007 as taught by Schmidt (*Nature*

Biotechnology, 2007, 25:273-275). As Schmidt discusses several RNAi patents, he points out that "Though RNAi has become invaluable for basic research, its therapeutic potential is unknown. Delivering RNAi drugs to target cells poses difficult challenges; largely because of this, drug-development with RNAi remains mainly in preclinical stages." (page 273)

With regard to the instantly claimed method wherein the retinitis is treated via intravitreal injection of siRNA, Schmidt teaches that siRNAs must reach internal organs through systemic delivery routes and this delivery problem still remains at large (page 275).

In light of the teachings of both Opalinska et al. and Schmidt, one of ordinary skill in the art would not have made and used the entire scope of the claimed invention solely based on the *in vitro* examples disclosed in the instant application. Further, the *in vitro* examples shown in the specification do not demonstrate any pharmaceutical effect that would render treatment of any CMV-associated disease effective. Since reduced IE2 expression levels are not indicative of treating a CMV-associated disease (e.g., retinitis, prostate cancer), and since there is neither positive *in vitro – in vivo* correlation nor sufficient *in vivo* data, and since the general teachings in the art are such that siRNA therapeutics remain unpredictable, one of ordinary skill in the art would not have made and used the instantly claimed pharmaceutical composition with a resultant therapeutic effect of treating a CMV-associated disease at the time the invention was made.

In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the Court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

In view of all the factors listed above and the totality of the teachings that the activity of siRNAs is unpredictable *in vivo*, undue experimentation would be required of a skilled artisan to practice the entire scope of the instantly claimed invention. Since the issues described above are not satisfactorily resolved herein, it is concluded, based on the evidence as a whole, that the instant specification fails to teach how to use the claimed invention without undue experimentation, and that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

Claims 1-7, 27-30, 38-45, 48-50, and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

In the instant case, the claims embrace any RNAi agent targeted to a CMV gene, which inhibits CMV in a CMV-infected cell; that is, the claims are directed to a genus of RNAi agents targeted to a CMV gene. As broadly claimed, the specification must provide sufficient distinguishing identifying characteristics of the genus by disclosing structure/function correlation of the claimed anti-CMV RNAi agents, particularly because of the unpredictability of

intracellular activities of siRNAs. See pages 5-6 above. The instant specification discloses only two siRNA species encompassed by the broadly claimed genus. Although Table II in the specification lists "genes to be targeted with siRNAs" and the "anticipated outcomes", conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of treating a subject comprising administering an RNAi agent targeted to a CMV gene. For an actual reduction to practice, the invention must have been sufficiently tested to demonstrate that it will work for its intended purpose, but it need not be in a commercially satisfactory stage of development. See, for example, *Scott v. Finney*, 34 F.3d 1058, 1062, 32 USPQ2d 1115, 1118-19 (Fed. Cir. 1994). Emphasis added by examiner.

Further, the claimed "RNAi agent" embraces any molecule that mediates RNAi, including siRNA, miRNA, and shRNA (see page 13 of the specification). However, the specification discloses only two siRNA molecules (SEQ ID NO:1 and SEQ ID NO:2) that target the claimed CMV gene with a resultant reduction of the CMV gene expression. As such, the two disclosed siRNA molecules comprising SEQ ID NO:1 and SEQ ID NO:2 are not representative number of species embraced by the claimed "RNAi agent that targets a CMV gene".

Note that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). See also MPEP §2163.

In light of the above, the instant specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented the genus claimed in the instant case. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (see page 1117).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 27-30, 45, 47-50, and 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (US 5,783,383) in view of Fire et al. (US 6,506,559 B1) and Tuschl et al. (US 7,056,704 B2).

The claims are drawn to a method of inhibiting a CMV *in vitro*, comprising exposing an infected cell to an RNAi agent that targets a CMV gene, wherein the gene is an IE2 gene, the RNAi agnet is a dsRNA molecule wherein each strand is about 18-29 nucleotides in length and has two 3'-deoxythimidines and a 5'-phosphate group, wherein the dsRNA comprises SEQ ID NO:2 in which T is replaced by U, the dsRNA is contained within an expression vector.

Kondo et al. teach that CMV is a significant pathogen in immuno-compromised individuals and one of the best studied virus in the art (column 2, lines 43-57). They teach the DNA sequence of IE2 transcript (column 3, lines 30-35). They teach a method of detecting CMV infection in a cell by PCR amplification using a reverse primer comprising SEQ ID NO:19 (column 4, lines 45-65; Figure 7). It is found that SEQ ID NO:19 of Kondo et al. is fully complementary to nucleotides 1-18 of the instantly claimed SEQ ID NO:2. They also teach expression vectors for expressing antisense RNA or ribozymes for gene inhibition applications (column 5, lines 1-47). Kondo et al. do not teach a method of inhibiting CMV expression comprising an RNAi agent.

Fire et al. teach that RNAi-mediated gene inhibition is advantageous over antisense approach because double-stranded RNA is more stable, the RNAi-mediated inhibition requires less concentration of the dsRNA for effective gene inhibition, and the RNAi-mediated inhibition occurs efficiently under physiological conditions (column 3, lines 20-45). They teach that the length of the double-stranded RNA is 25 nucleotides in length (column 8, lines 5-6). They teach that a gene derived from any pathogen in virus may be targeted for inhibition in cells *in vitro* such as HIV (column 8, lines 13-17; column 10, lines 8-18).

Tuschl et al. teach that dsRNA triggers RNAi and is process to 21-23 nucleotide RNA fragments in cells, thereby termed short interfering RNA (siRNA). See columns 1-2. They teach that siRNA of 19-25 nucletoides in length with 3'-deoxythymidine overhangs and 5'-phosphates mediate target-specific RNA interference (column 2, lines 35-67; column 3, lines 5-8; Figures 8B and 18-19). They teach that siRNAs comprise "U"s instead of "T"s. See Figures 5A and 8B. They teach that the thymidine overhang enhances nuclease resistance of siRNAs in cells and mediates more potent gene inhibition (column 22, lines 63-67; column 23, lines 1-4). They teach that the target gene may be a viral gene (column 5, lines 11-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the RNAi-mediated inhibition of Fire et al. to target the IE2 transcript of CMV of Kondo et al. by designing an siRNA molecule as taught by Tuschl et al.

One of ordinary skill in the art would have been motivated to so with a reasonable expectation of success because the CMV gene, especially the IE2 gene, was a well-known target for antisense-mediated gene therapy as taught by Kondo et al. (column 5, lines 1-47), and because targeting CMV or any viral pathogen via RNAi mechanism in cells *in vitro* was an art-recognized goal as taught by both Fire et al. (column 8, lines 13-17; column 10, lines 8-18) and Tuschl et al. (column 5, lines 11-15). Since Fire et al. expressly teach that RNAi-mediated gene inhibition is more potent and efficient than antisense-mediated gene inhibition (column 3, lines 20-45), the skilled artisan would have been motivated to replace the antisense-mediated CMV gene inhibition of Kondo et al. with the RNAi-mediated inhibition of Fire et al. Since both 3'-deoxythimidines and 5'-phosphate group were known to increase stability and efficacy of siRNAs as taught by Tuschl et al., the skilled artisan would have been further motivated to

incorporate such modifications into designing CMV siRNA molecules. Furthermore, the fully complementary sequence of the instantly claimed SEQ ID NO:2 was taught by Kondo et al. as an effective primer that amplifies the IE2 gene transcript. Although the primer sequence of Kondo et al. (SEQ ID NO:19) is complementary to nucleotides 1-18 of the 19-mer sequence of SEQ ID NO:2, one of ordinary skill in the art would have been motivated to modify the length of the anti-CMV siRNA molecule through routine optimization experimentation. Further, since the sequence of the IE2 transcript was taught by Kondo et al. (column 3, lines 30-35) and since the factors to consider in designing effective siRNAs (length limitations, modifications) were taught by Tuschl et al. (columns 2-3, 22-23), the skilled artisan would have had a reasonable expectation of success in making the siRNA comprising SEQ ID NO:2 with 3' and 5' modifications within the optimal range of length. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

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